(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
9 October 2003 (09.10.2003)

PCT

(10) International Publication Number
WO 03/082267 A1

(51) International Patent Classification[7]: A61K 31/40, 41/00, A61P 35/00

(21) International Application Number: PCT/EP03/03192

(22) International Filing Date: 17 March 2003 (17.03.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
02076240.7 2 April 2002 (02.04.2002) EP

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(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(regional)*: ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *with international search report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 03/082267 A1

(54) Title: COMBINED THERAPY AGAINST TUMORS COMPRISING SUBSTITUTED ACRYLOYL DISTAMYCIN DERIVATIVES AND RADIOTHERAPY

(57) Abstract: The present invention provides the use of acryloyl distamycin derivatives, in particular α-bromo- or α-chloro-acryloyl distamycin derivatives, in combination with radiotherapy, for the treatment of tumors.

COMBINED THERAPY AGAINST TUMORS COMPRISING SUBSTITUTED ACRYLOYL DISTAMYCIN DERIVATIVES AND RADIOTHERAPY

The present invention relates to the field of cancer treatment and provides an antitumor therapy comprising the combined use of a substituted acryloyl distamycin derivative, more particularly a α-bromo- or α-chloro-acryloyl-distamycin derivative, with radiotherapy.

The treatment of tumours with ionising radiation, also referred to as radiotherapy, is extensively used in cancer therapy as it provides destruction of tumour cells together with inhibition of tumour cell growth, presumably through DNA damage.

Some therapeutic compounds, which are known as being cytotoxic per se, hence susceptible of being used in the therapy of cancer, are also endowed with radiosensitisation activity as they are capable of inducing DNA radiation damage in response to ionizing radiation.

So far, the possibility of combining both cytotoxic agents, e.g. a given radiosensitiser and radiotherapy, with the expectation of getting a supra-additive antitumor effect in comparison to the single cytotoxics alone, is of utmost importance in cancer therapy.

Among the several compounds endowed with antitumor activity and also known as possessing radiosensitisation activity see, for instance, cisplatin, gemcitabine, navelbine, tomudex, nicotinamide, paclitaxel, docetaxel, simvastatin and topotecan.

In addition, the use of halogenated DNA ligands as possible radiosensitisers, also including some distamycin derivatives, were disclosed by R. Martin et al. in the international patent application WO 90/12321.

For a general reference to distamycin, an antibiotic substance with antiviral and antiprotozoal activity, as well as to the several derivatives thereof which are known as cytotoxic agents see, for instance, Nature 203: 1064 (1964); J. Med. Chem. 32: 774-778 (1989); and the international patent applications WO 90/11277, WO 98/21202, WO 99/50265, WO 99/50266 and WO 01/40181, all in the name of the applicant itself and herewith incorporated by reference.

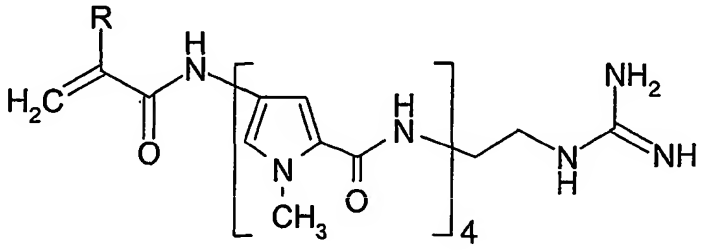
Among the several distamycin derivatives being disclosed so far, a class of α–bromo- or α-chloro-acryloyl-distamycins, as per the aforementioned international patent application WO 98/04524, were found to possess a significant antineoplastic activity.

We have now found that these same compounds are also unexpectedly endowed with a remarkable radiosensitisation activity which render their use, in combination with radiotherapy, particularly advantageous in cancer therapy.

It is therefore a first object of the present invention, the use of a α-bromo- or α–chloro-acryloyl-distamycin derivative in the preparation of a medicament having radiosensitisation activity.

In the present description, unless otherwise specified, with the term "radiosensitisation activity" it is intended the aforementioned capability of a compound, or medicament thereof, to act as a radiosensitiser. With the term "radiosensitiser", in its turn, we refer to a compound or medicament which is capable of increasing or otherwise improving tumor cells destruction in response to ionizing radiation.
Finally, the term "ionizing radiation" is the one conventionally adopted in the therapeutic field of cancer treatment and includes photons having enough energy for bonds ionization such as, for instance, α-, β- and γ-rays from radioactive nuclei as well as x-rays.

According to a preferred aspect of the invention, the α-bromo- or α–chloro-acryloyl-distamycin-derivative is a compound of formula (I) below



(I)

wherein R is a bromine or chlorine atom, more preferably bromine, or a pharmaceutically acceptable salt thereof.

Pharmaceutically acceptable salts of the compounds of formula (I) are the salts with pharmaceutically acceptable inorganic or organic acids such as, for instance, hydrochloric, hydrobromic, sulfuric, nitric, acetic, propionic, succinic, malonic, citric, tartaric, methanesulfonic, p-toluenesulfonic acid and the like; the hydrochloride salt being the preferred one.

Even more preferably, the acryloyl-distamycin derivative for use as radiosensitiser is the compound N-[5-[[[5-[[[2-[(aminoiminomethyl)amino]ethyl]amino]carbonyl]-1-methyl-1H-pyrrol-3-yl]amino]carbonyl]-1-methyl-1H-pyrrol-3-yl]-4-[[[4-[(2-bromo-1-oxo-2-propenyl)amino]-1-methyl-1H-pyrrol-2-yl]carbonyl]amino]-1-methyl-1H-pyrrole-2-carboxamide hydrochloride (internal code PNU 166196A).

The combined therapy of the invention is suitable for the treatment of various tumor forms such as, for instance, breast, ovary, lung, colon (including rectus), kidney, stomach, pancreas, liver, head and neck, esophagus, uterus (including body and cervix), vagina, melanoma and non malanoma skin cancer, as well as sarcomas.

From all of the above and unless otherwise specified, it is clear to the skilled person that the α–bromo- or α–chloro-acryloyl-distamycin derivative may be administered to mammals, including humans, through the usual routes, for example parenterally, e.g. by intravenous injection or infusion.

The dosage will depend from several factors, also including the selected schedule of administration which may comprise repeated doses, for instance once a day, once a week, twice a week, and the like, as the case may be.

As a non limiting example, suitable dosages may range from about 0.05 mg/m^2 to about 10 mg/m^2.

For any indication concerning suitable pharmaceutical forms for administering the acryloyl-distamycin derivatives in re, hence including any pharmaceutically acceptable excipient, see the aforementioned international patent application WO 98/04524.

A further aspect of the present invention is to provide a method of treating a mammal,

including humans, suffering from a neoplastic disease state, which method comprises administering to said mammal a α–bromo- or α–chloro-acryloyl-distamycin derivative and radiotherapy, in amounts and according to a schedule treatment effective to produce a synergistic antineoplastic effect.

By the term "synergistic" effect, as used herein, it is meant the inhibition of the growth tumor, preferably the complete regression of the tumor, by administering an effective amount of the above acryloyl distamycin derivative and the ionizing radiation to mammals, including humans. By the term "administered " or "administering", as used herein, it is meant parenteral (e.g. intravenous) administration.

As far as the schedule treatment is concerned, exposure to radiotherapy may either occur simultaneously whilst administering the medicament comprising the α-bromo- or α–chloro-acryloyl-distamycin derivative or, alternatively, sequentially in any order. Preferably, the schedule treatment first comprises administering the drug to the patient which only subsequently is subjected to radiotherapy exposure.

According to the present invention, the acryloyl distamycin derivative may be also administered with additional antitumor agents such as, for instance, topoisomerase I or II inhibitors, e.g. CPT-11, topotecan, 9-amino-camptothecin, 9-nitro-camptothecin, 10,11-methylenedioxy-camptothecin, doxorubicin, daunorubicin, epirubicin, nemorubicin, idarubicin, etoposide, teniposide, mitoxanthrone, losoxantrone, amsacrine, actinomycin D; alkylating agents, e.g. melphalan, chlorambucil, mechlorethamine, cyclophosphamide, ifosfamide, busulfan, carmustine, lormustine, semustine, fotemustine, decarbazine, temozolide, thitepa, mitomycin C, cisplatin, carboplatin, oxaliplatin, nedaplatin, lobaplatin; antimicrotubule agents, e.g. paclitaxel, docetaxel, vincristine, vinblastine, vindesine, vinorelbine, estramustine; antimetabolites, e.g. metotrexate, trimetrexate, tomudex, 5-FU, floxuridine, ftorafur, capecitabine, cytarabine, azacitidine, gemcitabine; protein kinase inhibitors, e.g. STI571 (Gleevec), ZD-1839 (Iressa), OSI-774 (Tarceva), SU 5416 (Semaxanib), SU 6668, SU 11248; retinoid

derivatives, e.g. cis-retinoic acids, trans-retinoic acids; cyclooxygenase inhibitors such as COX-2 inhibitors, e.g. celecoxib, rofecoxib, parecoxib, valdecoxib; hormonal agents, e.g. exemestane, formestane, atamestane, letrozole, fadrozole, anastrozole.

According to a preferred embodiment of the invention, the use of a α-bromo- or α-chloro-acryloyl-distamycin derivative with radiotherapy also comprises the administration of a platinum alkylating agent, more preferably cisplatin.

PHARMACOLOGY

The remarkable radiosensitisation effect exerted by the α-bromo- or α-chloro-acryloyl-distamycin derivatives, in particular the compounds of formula (I), is shown according to in vitro clonogenic assays on SQ20B (radiation-resistant human squamous cell carcinoma of the larynx) and A431 (human vulval carcinoma) cell lines. In this respect, two different schedule treatments were evaluated either comprising simultaneous exposure to the tested compound of formula (I) and to radiation, or sequential exposure to both these cytotoxic agents in any order, that is drug/radiation or radiation/drug (see details below). As control, the effect of cisplatin in combination with radiotherapy has been tested in the same operative conditions.

To define a Sensitization Ratio (SR), the clonogenic survival of cells being treated with a combination of irradiation and drug exposure (S_{X+D}) was compared with the product of survival for drug alone (S_D) and irradiation alone (S_X), as follows

$$SR = S_{X+D} / S_D * S_X$$

From the above, it is clear to the skilled person that if both radiation and drug exerted their cytotoxic effect independently from each other, SR values would be close to 1 whereas, on the contrary, a radiosensitisation effect indicating a synergism between ionizing radiation and drug is characterized by SR values lower than 1 ($SR < 1$).

Analysis of the obtained results in any of the experiments being carried out clearly indicate that the tested compound of formula (I) exerts a remarkable and statistically significant radiosensitising effect.

In particular, whilst sensitization is substantially comparable to that of cisplatin on SQ20B cell line, it is unexpectedly and significantly superior than that of cisplatin on A431 cell line, hence indicating a possible widest range of applications for the compounds of formula (I), in combination with radiotherapy.

In addition to the above, we unexpectedly found that the radiosensitisation effect of the compound of formula (I) could be even increased, to a statistically significant extent, when drug exposure occurred before irradiation treatment, according to one of the sequential schedule treatments.

To better illustrate the present invention, without posing any limitation to it, the following examples are now given.

Example 1

Radiosensitisation activity of PNU 166196A in comparison to cisplatin

For both compounds PNU 166196A and cisplatin, exposures were simultaneous to ionizing radiation in both SQ20B and A431 cell lines. The schedule consisted of 2 h drug treatment with a period of irradiation (10 minutes) starting at the beginning of the 2nd hour of treatment.

Four data sets for each of PNU 166196A and cisplatin, in each cell line were obtained (see table 1) comprising duplicates of two different drug concentration chosen to yield cytotoxicity values corresponding to 80% (C_{80}) and 20% (C_{20}) survival for treatment with the drug alone.

Table 1 - Sensitisation ratio of PNU 166196A and cisplatin in combination with radiotherapy

Cell line	Drug	Drug Concentration[a]	Sensitisazion Ratio SR[b]	
			Values for each culture	Mean of duplicates
SQ20B	PNU 166196A	50 (C_{80}) [c]	0.85	**C_{80} 0.85** **C_{20} 0.50**
		350 (C_{20}) [d]	0.46	
		50 (C_{80})	0.84	
		350 (C_{20})	0.55	p=0.017
	cisplatin	0.4 (C_{80})	0.78	**C_{80} 0.80** **C_{20} 0.77**
		6.5 (C_{20})	0.72	
		0.4 (C_{80})	0.82	
		6.5 (C_{20})	0.81	p=0.034
A431	PNU 166196A	20 (C_{80})	0.65	**C_{80} 0.62** **C_{20} 0.37**
		90 (C_{20})	0.33	
		20 (C_{80})	0.59	
		90 (C_{20})	0.40	p=0.029
	cisplatin	0.8 (C_{80})	1.02	**C_{80} 0.96** **C_{20} 0.97**
		5.0 (C_{20})	1.08	
		0.8 (C_{80})	0.84	
		5.0 (C_{20})	0.86	p=0.37

[a] Expressed as ng/ml for PNU 166196A and μM for cisplatin;

[b] SR values lower than 1 (SR < 1) indicate radiosensitisation;

[c] C_{80} drug concentration corresponding to 80% cell survival

[d] C_{20} drug concentration corresponding to 20% cell survival

From the above, SR for PNU 166196A is lower than 1 in both cell lines being investigated; on A431, SR for PNU 166196 is markedly lower than that of cisplatin, hence indicating a superior radiosensitisation effect.

Example 2

Radiosensitisation activity of PNU 166196A under sequential schedule treatment

PNU 166196A was tested in both SQ20B and A431 cell lines, according to two sequential schedule treatments comprising: 2 h drug treatment ending 60 minutes before irradiation (drug-before schedule) and 2 h drug treatment starting 40 minutes after

irradiation (drug-after schedule), the irradiation period being of 10 minutes, in each case. For each cell line, PNU 166196A was tested at the highest concentration (see table 2) to yield cytotoxicity values corresponding to 20% (C_{20}) survival for treatment with the drug alone.

Table 2 - Effect of the sequence of treatment on the sensitisation ratio of PNU 166196 in combination with radiotherapy

Cell line	Drug Concentration (ng/ml)	Sensitisazion Ratio SR [a]	
		Drug-before [b]	Drug-after [c]
SQ20B	350 (C_{20}) [d]	**0.15**	0.62
	350 (C_{20})	**0.47**	0.73
A431	90 (C_{20})	**0.11**	0.87
	90 (C_{20})	**0.13**	0.43
Paired t-test		P=0.043	P=0.074

[a] SR values lower than 1 (SR < 1) indicate radiosensitisation;

[b] 2 h exposure to PNU 16196A before irradiation;

[c] 2 h exposure to PNU 16196A after irradiation;

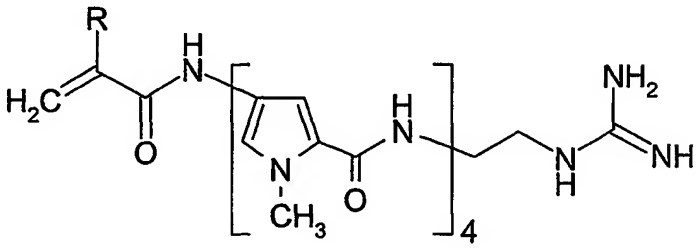
[d] C_{20} drug concentration corresponding to 20% cell survival

From the above, even if SR values are lower than 1 in both cell lines and according to both schedules, the radiosensitisation activity of PNU 166196A is significantly higher (SR<<1) when the treatment with the compound is carried out before irradiation.

CLAIMS

1. Use of a α-bromo- or α–chloro-acryloyl-distamycin derivative in the preparation of a medicament having radiosensitisation activity.

2. Use according to claim 1 wherein the α-bromo- or α–chloro-acryloyl-distamycin derivative is of formula (I)



(I)

wherein R is a bromine or chlorine atom, or a pharmaceutically acceptable salt thereof.

3. Use according to claim 2 wherein, within formula (I), R is a bromine atom.

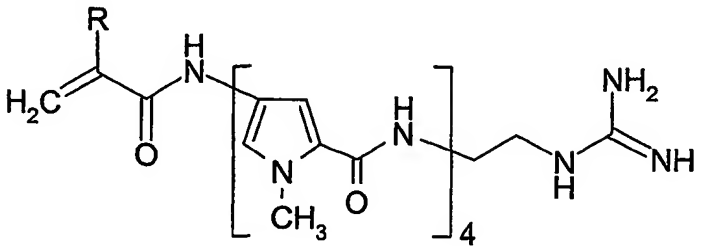
4. Use according to claim 1 wherein the acryloyl-distamycin derivative is the compound N-[5-[[[5-[[[2-[(aminoiminomethyl)amino]ethyl]amino]carbonyl]-1-methyl-1H-pyrrol-3-yl]amino]carbonyl]-1-methyl-1H-pyrrol-3-yl]-4-[[[4-[(2-bromo-1-oxo-2-propenyl)amino]-1-methyl-1H-pyrrol-2-yl]carbonyl]amino]-1-methyl-1H-pyrrole-2-carboxamide hydrochloride.

5. Use according to claim 1 for the treatment of tumors selected from the group consisting of breast, ovary, lung, colon (including rectus), kidney, stomach, pancreas, liver, head and neck, esophagus, uterus (including body and cervix), vagina, melanoma and non malanoma skin cancer, as well as sarcomas.

6. A method of treating a mammal, including humans, suffering from a neoplastic disease state, which method comprises administering to said mammal a α–bromo- or α–chloro-acryloyl-distamycin derivative in combination with radiotherapy, in amounts

and according to a schedule treatment effective to produce a synergistic antineoplastic effect.

7. The method of claim 6 wherein the α-bromo- or α–chloro-acryloyl-distamycin derivative is of formula (I)



(I)

wherein R is a bromine or chlorine atom, or a pharmaceutically acceptable salt thereof.

8. The method of claim 7 wherein, within formula (I), R is a bromine atom.

9. The method of claim 6 wherein the acryloyl-distamycin derivative is the compound N-[5-[[[5-[[[2-[(aminoiminomethyl)amino]ethyl]amino]carbonyl]-1-methyl-1H-pyrrol-3-yl]amino]carbonyl]-1-methyl-1H-pyrrol-3-yl]-4-[[[4-[(2-bromo-1-oxo-2-propenyl)amino]-1-methyl-1H-pyrrol-2-yl]carbonyl]amino]-1-methyl-1H-pyrrole-2-carboxamide hydrochloride.

10. The method of claim 6 wherein the neoplastic disease state is selected from the group consisting of breast, ovary, lung, colon (including rectus), kidney, stomach, pancreas, liver, head and neck, esophagus, uterus (including body and cervix), vagina, melanoma and non malanoma skin cancer, as well as sarcomas.

11. The method of claim 6 wherein exposure to radiotherapy occurs either simultaneously whilst administering the medicament of claim 1, or sequentially, in any order.

12. The method of claim 6 first comprising administering the α-bromo- or α–chloro-

acryloyl-distamycin derivative to the patient and subsequently subjecting the said patient to radiotherapy.

13 The method according to claims 6 optionally further comprising the administration of an additional antitumor agent, either separately, simultaneously or sequentially, in any order.

14 The method of claim 13 wherein the additional antitumor agent is selected from the group consisting of topoisomerase I or II inhibitors, alkylating agents, antimicrotubule agents, antimetabolites, protein kinase inhibitors, retinoid derivatives, cyclooxygenase inhibitors and hormonal agents.

15 The method of claim 14 wherein the additional antitumor agent is cisplatin.

16 A pharmaceutical composition comprising a α-bromo or α-chloro-acryloyl-distamycin derivative of formula (I) or pharmaceutically acceptable salt thereof, as defined in claim 2, for use as a radiosensitizer

17 The pharmaceutical composition of claim 16 wherein the derivative of formula (I) is as defined in claim 4.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/03192

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/40 A61K41/00 A61P35/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, CHEM ABS Data, BIOSIS, EMBASE, CANCERLIT, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 04524 A (CALDARELLI MARINA ;BERIA ITALO (IT); COZZI PAOLO (IT); CAPOLONGO L) 5 February 1998 (1998-02-05) cited in the application claims 3,5,6,8	16,17
X	MARCHINI S ET AL: "Development of distamycin-related DNA binding anticancer drugs." EXPERT OPINION ON INVESTIGATIONAL DRUGS. ENGLAND SEP 2001, vol. 10, no. 9, September 2001 (2001-09), pages 1703-1714, XP002243510 ISSN: 1354-3784	16,17
A	abstract page 1710 -page 1711	1-15

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
5 June 2003	24/06/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,	Pacreu Largo, M

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/03192

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
A	WO 01 97790 A (BERIA ITALO ;COZZI PAOLO (IT); GERONI MARIA CRISTINA ROSA (IT); PH) 27 December 2001 (2001-12-27) claims	13-15

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 03/03192

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: -
because they relate to subject matter not required to be searched by this Authority, namely:

see FURTHER INFORMATION sheet PCT/ISA/210

2. [X] Claims Nos.: -
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.1

Although claims 6 to 15 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Continuation of Box I.1

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

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Continuation of Box I.2

The expression "alfa-bromo- or alfa-chloro-acryolyl-distamycin derivative" in claims 1 and 6 relate to an extremely large number of possible compounds. In fact, the claims contain so many options and variables that a lack of clarity and conciseness within the meaning of Article 6 PCT arises to such an extent as to render a meaningful search of the claims impossible.

Consequently, the search has been carried out for those parts of the application which do appear to be clear and concise, namely the compounds of formula (I) as disclosed in claim 2 and the specific compound of claim 4.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/03192

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